

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
James Berger Camden et al.

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(in parent appl'n: P. Spivack)

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(in parent appl'n: 1614)

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For: Viral Treatment

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Commissioner of Patents
Washington, D.C. 20231

Sir:

PRELIMINARY AMENDMENT

This Preliminary Amendment is being filed concurrently with a Request to File a Divisional Application. Please amend the application as indicated below.

AMENDMENT

Attached is a marked-up version of amended specification paragraphs and amended claims where language deleted is in brackets, and language added is underlined.

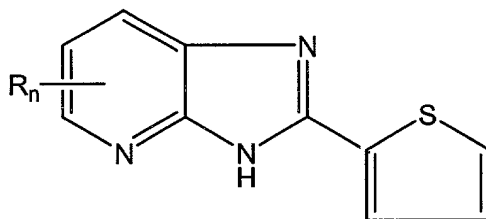
In the Specification:

The priority paragraph at page 1, line 8 has been rewritten to read:

The present application is a divisional application of USSN 09/538,006 filed March 29, 2000 from which priority under 35 U.S.C. §120 is claimed. USSN 09/538,006 is a continuation in part of application of J.B. Camden, serial number 09/281,892, filed March 31, 1999.

The paragraph beginning on page 3, line 22, is amended to read:

A pharmaceutical composition for treatment of viral infections in patients in need thereof, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount of an anti-viral compound having the formula:



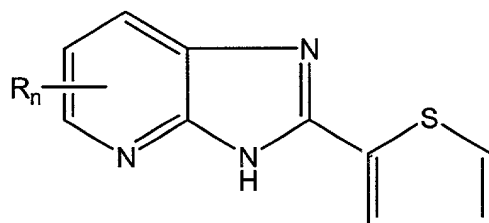
wherein n is 1 to 3; and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, its prodrugs and pharmaceutically acceptable salts.

The paragraph beginning on page 4, line 12, is amended to read:

These materials are active against *Cryptococcus neoformans* and *Curvularia lunata*. Both of these are fungi which are found in AIDS patients.

The paragraph beginning on page 5, line 23, is amended to read:

As used herein, the "thienyl imidazolo[4,5]pyridine derivatives" or "2-thienyl imidazolo[4,5]pyridine compounds" or "2-(2-thienyl)imidazolo[4,5-b]pyridine compounds" are the members of the group of compounds having the formula:



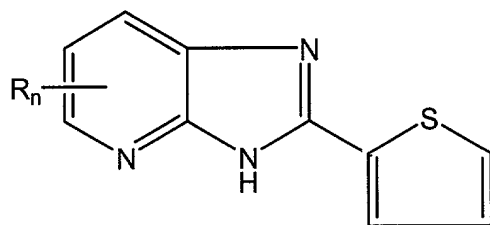
wherein n is 1-3; and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, its prodrugs and pharmaceutically acceptable salts.

The paragraph beginning at page 6, line 28, is amended to read:

As used herein "viruses" includes viruses which infect animals or mammals, including humans. Viruses include retroviruses, HIV, influenza, polio viruses, herpes simplex, hepatitis B, hepatitis C, other hepatitis viruses, Kaposi's sarcoma virus, rhinoviruses, bovine diarrhea virus, and the like. HIV and AIDS are immunosuppressant diseases.

The paragraph beginning at page 7, line 7, is amended to read:

The 2-thienyl imidazolo[4,5]pyridine compounds useful herein have the formula:



wherein n is 1-3; and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, preferably from 1 to 6. Preferably the 2-thienyl imidazo[4,5]pyridine is substituted with an alkyl of less than 4 carbons, a halogen (preferably a chloro), nitro, hydroxy or oxychloro in the 7 or 8 position and the remaining substituents of the pyridine ring are hydrogen.

The paragraph beginning at page 32, line 24, is amended to read:

2-(2-thienyl)imidazo[4,5-b]pyridine was tested against Kaposi's Sarcoma, a herpes virus, in vitro using the Human Herpes Virus 8 (HHV8) cell line, TPA-induced BCBL-1 cells. The DNA copy number and the toxicity value were measured and compared with Cidofovir. Kaposi's sarcoma (KS) is a cancer that is often found in people with weak immune systems, such as those taking immunosuppressants or those with AIDS. The exact nature of the disease is uncertain, but it is almost always found in association with HHV8. Recent studies suggest that KS is caused by the herpes virus; that is, that KS is a herpes virus that manifests itself as a cancer.

The paragraph beginning at page 34, line 3, is amended to read:

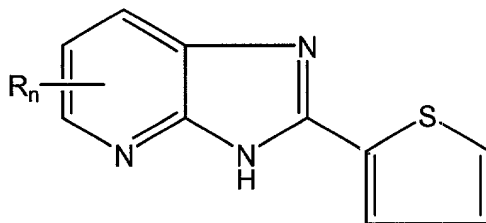
2-(2-thienyl)imidazo[4,5-b]pyridine was tested against a number of fungi *in vitro*. It was active against *Cryptococcus neoformans* and *Curvularia lunata*. The cidal activity for the *C. neoformans* is high enough that it is clear static against this yeast. This test was conducted using a method based upon NCCLS reference method M-27A published in 1997. Solvent, medium and growth controls were set-up with the tests. Once these were read to validate the test performance, the QC fungi were read to insure they had expected results. These steps validated the test system. DMSO was used as a drug-chemical solvent. These tests were read following incubation at 35°C when the QC organisms (*Candida* spp.) showed good growth. MIC values were concentrations in which growth was inhibited or reduced at least 90% in comparison to the control growth. The 90% cut-off is necessary for azoles, which are static and not cidal. The FMC or cidal level was determined by sub-culturing a sample from each tube showing no growth.

In the Claims:

Cancel claims 1-19, without prejudice.

The following claims 20 and 22-26 are amended, as indicated in the attached marked up version:

20. (1st Time Amended) A pharmaceutical composition comprising a therapeutically effective amount of a 2-thienyl imidazo[4,5]pyridine having the formula:



wherein,

n is from 1 to 3; and

R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6.

22. (1st Time Amended) A pharmaceutical composition according to Claim 28 wherein said pharmaceutical addition salt is selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, cintrates, benzoates, salicylates, ascorbates, and mixtures thereof.

23. (1st Time Amended) A pharmaceutical composition according to Claim 22 comprising from about 150 mg to about 5000 mg of said 2-thienyl imidazo[4,5]pyridine.

24. (1st Time Amended) A pharmaceutical composition according to Claim 23 which further comprises a pharmaceutical carrier.

25. (1st Time Amended) A pharmaceutical composition according to Claim 24 which is in a solid form wherein said pharmaceutical carrier is selected from the group consisting of lactose, sucrose, gelatin, cyclodextrin, substituted cyclodextrin, and agar.

26. (1st Time Amended) A pharmaceutical composition according to Claim 25 which is in a liquid form wherein said liquid form is selected from the group consisting of an aqueous solution, an emulsion, a suspension solution, a suspension reconstituted from non-effervescent or effervescent preparations, and a suspension in pharmaceutically acceptable fats or oils.

Please add the following Claims 28-44, as indicated below:

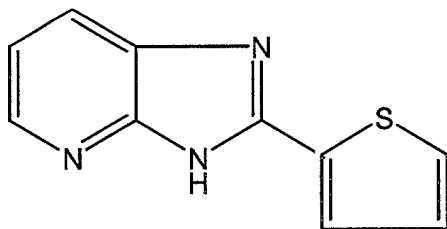
--28. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a pharmaceutical addition salt thereof.

29. A pharmaceutical composition according to Claim 28 wherein said pharmaceutical addition salt is a chloride.

30. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a prodrug thereof.

31. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a liposome delivery system.

32. A pharmaceutical composition comprising a therapeutically effective amount of 2-(2-thienyl)imidazolo[4,5-b]pyridine, having the formula:



33. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazolo[4,5-b]pyridine is in the form of a pharmaceutical addition salt thereof.

34. A pharmaceutical composition according to Claim 33 wherein said pharmaceutical addition salt is a hydrochloride salt.

35. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazo[4,5-b]pyridine is in the form of a prodrug thereof.

36. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazo[4,5-b]pyridine is in the form of a liposome delivery system.

37. A pharmaceutical composition according to Claim 32 comprising a pharmaceutical carrier and from about 1 mg to about 600 mg of said 2-(2-thienyl)imidazo[4,5-b]pyridine.

38. A pharmaceutical composition according to Claim 37 wherein said pharmaceutical carrier is selected from the group consisting of lactose, sucrose, gelatin, cyclodextrin, substituted cyclodextrin, agar, an aqueous solution, an emulsion, a suspension solution, a suspension reconstituted from non-effervescent or effervescent preparations, and a suspension in pharmaceutically acceptable fats or oils.

39. A pharmaceutical composition according to Claim 20 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.

40. A pharmaceutical composition according to Claim 32 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.

41. A pharmaceutical composition according to Claim 20 which further comprises a therapeutic agent.

42. A pharmaceutical composition according to Claim 41 wherein said therapeutic agent is selected from the group consisting of AZT, TC-3, protease inhibitors, acyclovir, famciclovir, valacyclovir, Ribavirin, interferon, a combination of Ribavirin and interferon, a combination of Ribavirin and beta globulin, a recombinant alpha interferon, and mixtures thereof.

43. A pharmaceutical composition according to Claim 41 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.

44. A pharmaceutical composition according to Claim 43 wherein said viral infection is HIV and said therapeutic agent is selected from the group consisting of AZT, TC-3, and protease inhibitors.--

REMARKS

I. Status of the Application

Claims 1-19 are canceled without prejudice, as being directed to an invention previously elected in the parent application.

Claims 20 and 22-26 have been amended to correct certain inadvertent typographical errors and to more clearly claim that which Applicants consider to be the invention.

Language of amended claims and added Claims 28-44 find support in the specification as originally filed. No new matter has been added by the amended or added claims.

The specification is amended throughout to correct an inadvertent typographical error with respect to the value of "n", and to correct other inadvertent typographical or spelling errors. It is further amended to clarify the relationship between Kaposi's sarcoma and the herpes virus HHV8. No new matter has been added to the specification by the amendments.

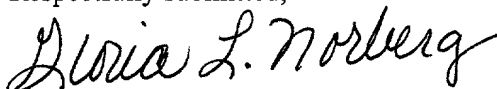
II. Information Disclosure Statement

An IDS is forwarded herewith under 37 CFR 1.97(b)(1). It is respectfully requested that the Examiner review the IDS and make it of record in this application.

III. Conclusion

Consideration and an early indication of the allowability of Claims 20-44 are earnestly requested. Should the Examiner have any questions, comments or suggestions that would expedite the prosecution of the present case to allowance, Applicants' representative, Dr. Rose Ann Dabek, earnestly requests a telephone conference at (513) 627-8824.

Respectfully submitted,



Gloria L. Norberg
Reg. No. 36,706

Date: January 11, 2001

Akin, Gump, Strauss, Hauer & Feld, L.L.P.
1900 Frost Bank Building
816 Congress Avenue
Austin, Texas 78701
Telephone: (512) 499-6200

MARKED-UP VERSION OF AMENDMENTS TO SPECIFICATION AND CLAIMS

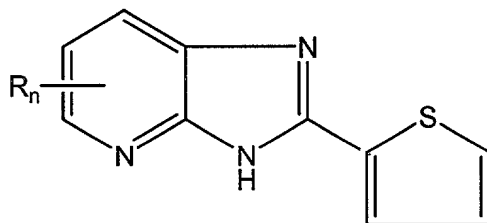
In the Specification:

At page 1, line 8, please delete "this application" and insert:

--The present application is a divisional application of USSN 09/538,006 filed March 29, 2000 from which priority under 35 U.S.C. §120 is claimed. USSN 09/538,006--

The paragraph beginning on page 3, line 22, is amended to read:

A pharmaceutical composition for treatment of viral infections in patients in need thereof, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount of an anti-viral compound [selected from the group consisting of] having the formula:



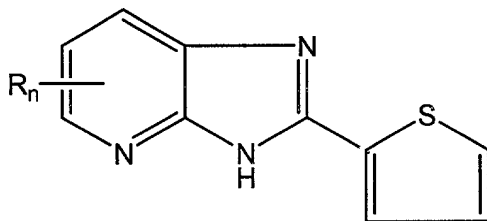
wherein n is 1 to [4,] 3[,] and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, [or] fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, its prodrugs and pharmaceutically acceptable salts.

The paragraph beginning on page 4, line 12, is amended to read:

These materials are active against [cryptococcus] Cryptococcus *neoformas* and [curvularia] Curvularia *lunata*. Both of these are fungi which are found in [AIDs] AIDS patients.

The paragraph beginning on page 5, line 23, is amended to read:

As used herein, the "thienyl[-]imidazolo[][4,5]pyridine derivatives" or "2-thienyl[-]imidazolo[][4,5]pyridine compounds" or "2-(2-thienyl)imidazolo[4,5-b]pyridine compounds[are derivatives]" are the members of the group of compounds having the formula:



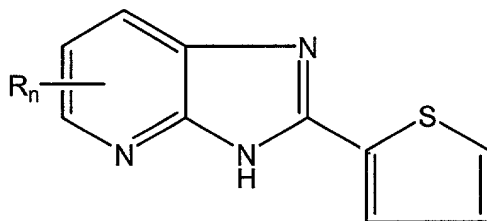
wherein n is 1-[4,]3;[,] and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, [or] fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, its prodrugs and pharmaceutically acceptable salts.

The paragraph beginning at page 6, line 28, is amended to read:

As used herein "viruses" includes viruses which infect animals or mammals, including humans. Viruses include retroviruses, HIV, influenza, polio viruses, herpes simplex, hepatitis B, hepatitis C, other hepatitis viruses, Kaposi's sarcoma virus, rhinoviruses, bovine diarrhea virus, and the like. HIV and AIDS are immunosuppressant diseases.

The paragraph beginning at page 7, line 7, is amended to read:

The 2-thienyl[-] imidazo[] [4,5]pyridine compounds useful herein have the formula:



wherein n is 1-[4,]3;[,] and R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, [or] fluoro, oxychloro, hydroxy, sulfhydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from 0 to 6, preferably from 1 to 6. Preferably the [2-(2-thienyl) imidazo[4,5-b]pyridine] 2-thienyl imidazo[4,5]pyridine is substituted with an alkyl of less than 4 carbons, a halogen[,] (preferably a chloro), nitro, hydroxy or oxychloro in the 7 or 8 position and the remaining substituents of the pyridine ring are hydrogen.

The paragraph beginning at page 32, line 24, is amended to read:

2-(2-thienyl)[-] imidazo[] [4,5-b]pyridine was tested against Kaposi's Sarcoma, a herpes virus, in vitro using the Human Herpes Virus 8 (HHV8) cell line, TPA-induced BCBL-1 cells. The DNA copy number and the toxicity value were measured and compared with Cidofovir. Kaposi's sarcoma (KS) is a cancer that is often found in people with weak immune systems, such as those taking immunosuppressants or those with AIDS. The exact nature of the disease is uncertain, but it is almost always found in association with HHV8. Recent studies suggest that KS is caused by the herpes virus; that is, that KS is a herpes virus that manifests itself as a cancer.

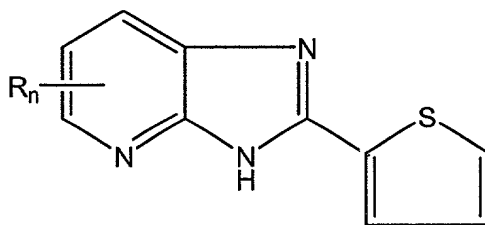
The paragraph beginning at page 34, line 3, is amended to read:

2-(2-thienyl)-imidazo[4,5-b]pyridine was tested against a number of fungi *in vitro*. It was active against [*cryptococcus*] *Cryptococcus neoformans* and [*curvularai*] *Curvularia lunata*. The cidal activity for the *C. neoformans* is high enough that it is clear static against this yeast. This test was conducted using a method based upon NCCLS reference method M-27A published in 1997. Solvent, medium and growth controls were set-up with the tests. Once these were read to validate the test performance, the QC fungi were read to insure they had expected results. These steps validated the test system. DMSO was used as a drug-chemical solvent. These tests were read following incubation at 35°C when the QC organisms (*Candida* spp.) showed good growth. MIC values were concentrations in which growth was inhibited or reduced at least 90% in comparison to the control growth. The 90% cut-off is necessary for azoles, which are static and not cidal. The FMC or cidal level was determined by sub-culturing a sample from each tube showing no growth.

In the Claims:

The following claims 20 and 22-26 are amended as indicated:

20. (1st Time Amended) A pharmaceutical composition [for treating viral infections] comprising a therapeutically effective amount of a 2-thienyl imidazo[4,5]pyridine having the formula:



wherein,

n is from 1 to [4,] 3; and

R is selected from the group consisting of hydrogen, alkyl having from 1 to 7 carbon atoms, chloro, bromo, [or] fluoro, oxychloro, hydroxy, [sulphydryl] sulphydryl, and alkoxy having the formula $-O(CH_2)_yCH_3$ wherein y is from [1] 0 to 6[, and the pharmaceutically acceptable salts thereof].

22. (1st Time Amended) A pharmaceutical composition according to Claim [20] 28 wherein said pharmaceutical [acceptable acid] addition salt[s are] is selected from the group consisting of chlorides,

bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, cintrates, benzoates, salicylates, ascorbates, and mixtures thereof.

23. (1st Time Amended) A pharmaceutical composition according to Claim 22 comprising from about 150 mg to about 5000 mg of said 2-thienyl[-] imidazolo[][4,5]pyridine.

24. (1st Time Amended) A pharmaceutical composition according to Claim 23 [wherein said composition] which further comprises a pharmaceutical carrier.

25. (1st Time Amended) A pharmaceutical composition according to Claim 24 which is in a solid form [comprising a] wherein said pharmaceutical carrier is selected from the group consisting of lactose, sucrose, gelatin, cyclodextrin, substituted cyclodextrin, and agar.

26. (1st Time Amended) A pharmaceutical composition according to Claim 25 which is in a liquid form wherein said liquid [dosage] form is selected from the group consisting of an aqueous solution[s], an emulsion[s], a suspension solution[s], [and] a suspension reconstituted from non-effervescent [and] or effervescent preparations, and a suspension in pharmaceutically acceptable fats or oils.

Please add the following Claims 28-44, as indicated below:

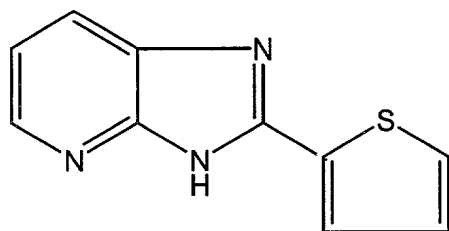
--28. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a pharmaceutical addition salt thereof.

29. A pharmaceutical composition according to Claim 28 wherein said pharmaceutical addition salt is a chloride.

30. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a prodrug thereof.

31. A pharmaceutical composition according to Claim 20 wherein said 2-thienyl imidazolo[4,5]pyridine is in the form of a liposome delivery system.

32. A pharmaceutical composition comprising a therapeutically effective amount of 2-(2-thienyl)imidazolo[4,5-b]pyridine, having the formula:



33. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazo[4,5-b]pyridine is in the form of a pharmaceutical addition salt thereof.
34. A pharmaceutical composition according to Claim 33 wherein said pharmaceutical addition salt is a hydrochloride salt.
35. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazo[4,5-b]pyridine is in the form of a prodrug thereof.
36. A pharmaceutical composition according to Claim 32 wherein said 2-(2-thienyl)imidazo[4,5-b]pyridine is in the form of a liposome delivery system.
37. A pharmaceutical composition according to Claim 32 comprising a pharmaceutical carrier and from about 1 mg to about 600 mg of said 2-(2-thienyl)imidazo[4,5-b]pyridine.
38. A pharmaceutical composition according to Claim 37 wherein said pharmaceutical carrier is selected from the group consisting of lactose, sucrose, gelatin, cyclodextrin, substituted cyclodextrin, agar, an aqueous solution, an emulsion, a suspension solution, a suspension reconstituted from non-effervescent or effervescent preparations, and a suspension in pharmaceutically acceptable fats or oils.
39. A pharmaceutical composition according to Claim 20 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.
40. A pharmaceutical composition according to Claim 32 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.

41. A pharmaceutical composition according to Claim 20 which further comprises a therapeutic agent.

42. A pharmaceutical composition according to Claim 41 wherein said therapeutic agent is selected from the group consisting of AZT, TC-3, protease inhibitors, acyclovir, famciclovir, valacyclovir, Ribavirin, interferon, a combination of Ribavirin and interferon, a combination of Ribavirin and beta globulin, a recombinant alpha interferon, and mixtures thereof.

43. A pharmaceutical composition according to Claim 41 used to treat a viral infection wherein said viral infection is selected from the group consisting of HIV, herpes simplex, hepatitis, and HHV8.

44. A pharmaceutical composition according to Claim 43 wherein said viral infection is HIV and said therapeutic agent is selected from the group consisting of AZT, TC-3, and protease inhibitors.--

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